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Specialty Conference

Early Diagnosis of Chronic Obstructive Lung Disease

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Participants: RICHARD H. GREENSPAN, M.D., WARREN M. GOLD M.D., AND ALLAN B. COHEN, M.D.

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DR. MURRAY:* This symposium will be devoted to the early diagnosis, treatment, and prevention of chronic obstructive lung diseases. The topic is a timely one because it has been said that we are in a virtual epidemic of these diseases, and, accordingly, they have assumed enormous medical, sociologic and economic importance. I say "these diseases" because chronic obstructive lung disease is really a generic term that includes at least four separate disease entities: pulmonary emphysema, chronic bronchitis, bronchial asthma, and, occasionally, bronchiectasis.

The fact that these fundamentally different disease processes were lumped together in a general category about 15 years ago is an indication of our ignorance at the time. They were classified together because they had many similar clinical manifestations, and they all manifested a common hallmark—obstruction to expired air flow. One of the important points that we will emphasize in this symposium is that it is now possible by the application of sophisticated biochemical, radiographic, and physiologic studies to differentiate these separate entities.

The reason for stressing early diagnosis is shown in Chart 1, which depicts schematically the course of a patient with either chronic bronchitis or emphysema from its onset, through a period of increasing severity, until the death of the patient. Although good data on the natural history of these diseases are not available, there is evidence that in the later stages of the disorders there is a relatively uniform (linear) progressive decline in pulmonary function. If we extrapolate backward from the data obtained in the advanced stages of these illnesses, we can infer that their total duration is 30 or 40 years or longer. This assumption is supported by the pathologic studies of Kleinerman, Cowdrey and Stein.[1] When they examined the lung specimens of 101 subjects between the ages of 15 and 44 years who died suddenly from trauma or accidental death they found anatomic evidence of emphysema in the lungs of the youngest age group studied, and the extent and severity of these lesions increased with advancing age.

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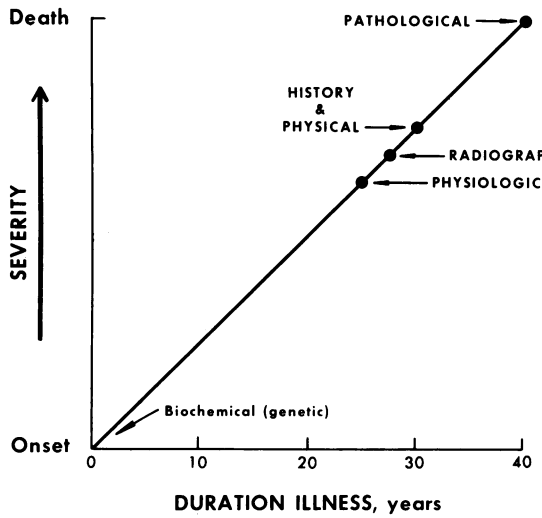

Chart 1.—A schematic depiction of the time-course of a patient with either chronic bronchitis or emphysema from the onset of the disease through a period of increasing severity to death. The earliest time when diagnosis is possible by various techniques is shown.

In the early 1900's the diagnosis of the various forms of chronic obstructive lung disease was uncommon and was determined largely by pathologists at the autopsy table. Even then the incidence of the disease was probably greatly underestimated, owing to faulty techniques of lung fixation and examination. In the 1930's and 1940's reliance was placed on conventional clinical techniques and it became evident that these allow us to diagnose the illnesses only when they are in an advanced state. Early diagnosis was impossible by these methods because, owing to the great reserve capacity of the lung, neither signs nor symptoms are produced until extensive parenchymal damage or airway involvement has occurred. Another point that we will emphasize in this symposium is that with new and available techniques of radiographic, physiologic and biochemical examination the diagnostic threshold can be lowered, permitting us to make the diagnosis much earlier in the long course of these illnesses. We believe early recognition will allow us to institute appropriate therapy that will forestall or retard the inexorable tendency of these diseases to progress. The first discussant is Dr. Richard Greenspan, who will comment on the usefulness of various radiographic techniques for the diagnosis of chronic obstructive lung diseases and describe the value of timed expiratory chest films for detection of obstructive pulmonary disease.

DR. GREENSPAN:† The chest roentgenogram is universally utilized to evaluate normal and abnormal morphologic features of the lungs. However, as a diagnostic test for the detection of obstructive pulmonary disease it is very crude. It is only of value in detecting advanced cases in which pronounced morphologic change in lung structure has already occurred. Roentgenographic-pathologic studies reported in the literature emphasize this point.[2-6] Since the diagnosis of early obstructive lung disease depends on airflow and volume studies, any single static measurement could be expected to be of limited value.

Comparison of a chest roentgenogram obtained during expiration with a standard inspiration film increases the sensitivity of roentgenographic diagnosis of obstructive pulmonary disease, but it is still only of value in moderately advanced and advanced cases. The main drawback is that the time required for the patient to expel air between inspiration and expiration remains unknown.

In an effort to increase further the sensitivity of radiography in diagnosing obstructive pulmonary disease, we developed a method to obtain timed films at full inspiration, at forced expiratory volume in 1 second (FEV_1), and at full expiration—the same measurements that are used clinically in screening for obstructive airway disease.[7] A simple modification of a spirograph and an x-ray generator is utilized. The patient is first instructed on how to use a spirometer, and several control spirograms are obtained. He then stands in front of an x-ray film changer with the mouthpiece of the spirometer in place, and a full inspiratory chest roentgenogram is obtained. The patient then performs a forced vital capacity maneuver, blowing the air out into the spirometer. The timing device attached to the spirometer is automatically activated when expiration commences, and 1 second later a radiographic exposure is triggered (the FEV_1 film). The third chest film is taken on completion of the forced vital capacity maneuver. Thus, we not only have films taken at full inspiration, at FEV_1 and at full expiration, but we also have the spirographic trace, obtained simultaneously with

†Richard H. Greenspan, M.D., Professor of Radiology, University of California, San Francisco. The studies discussed herein were carried out in collaboration with Stuart S. Sagel, M.D. (NIH Fellow in Academic Radiology, GM 01272); James McMahon (Medical Student); and Gordon Gamsu, M.D. (Fellow of the James Picker Foundation).

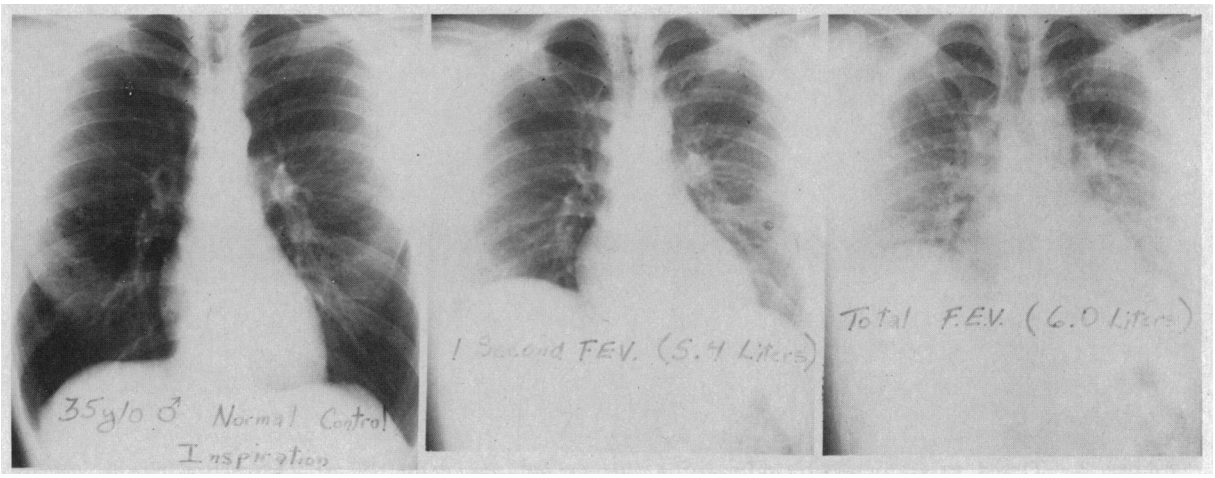

Figure 1.—Timed expiratory chest films of a normal 35-year-old man. The majority of diaphragmatic motion occurs between the inspiration film and the FEV_1 film, during which time the patient expired 5.4 liters of air. Slight change occurs between the FEV_1 and the total FEV films, with another 0.6 liters of air being expelled. The mediastinum remains in the midline.

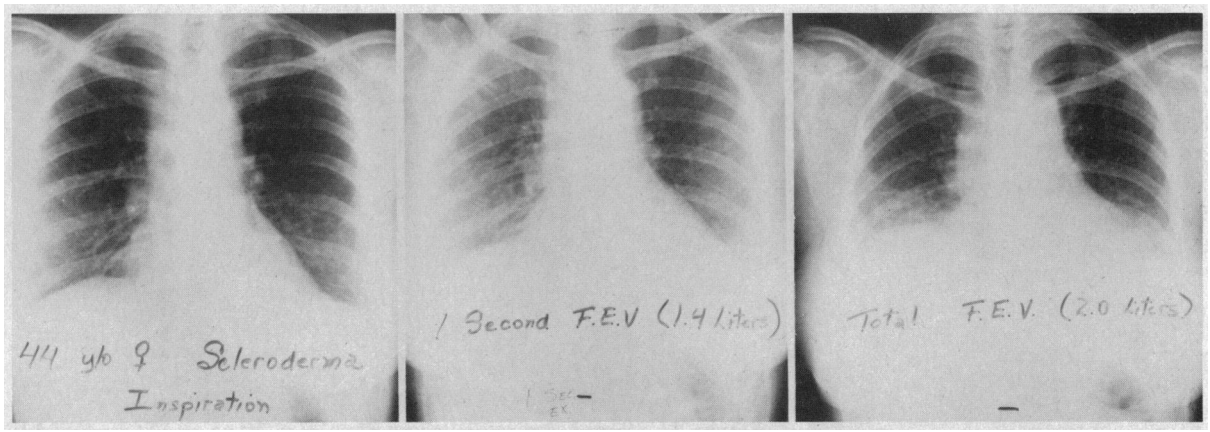

Figure 2.—Timed expiratory chest films of a 44-year-old woman with restrictive disease from scleroderma. Relatively little diaphragmatic motion occurs. The majority of the motion, however, is between the inspiration and the FEV_1 film. Total vital capacity is 2.0 liters. No mediastinal shift or evidence for localized air trapping is seen.

the roentgenograms, and a marker on the trace to ensure that the FEV_1 film actually was taken 1 second after start of expiration.

Although more than 150 patients have thus far been examined by this method, the films and spirographic tracings of only 90 have been carefully analyzed. The preliminary results in this pilot group indicate that this modification of standard x-ray techniques is of value. Of 28 normal control subjects, five had timed expiratory chest films indicative of either obstructive or restrictive pulmonary disease, which was subsequently confirmed by examination of the spirometric tracing. Forty-three of 44 patients with abnormal spirographic records had abnormal chest films as well. Six patients showed evidence of localized trapping of air on the 1 second FEV film that could not be appreciated on either the full inspiration or full expiration x-ray examination; three of these had normal spirometric records.

In a normal subject, the major change in the position of the diaphragms and in the chest volume occurs between the inspiration and the FEV_1 films, with only a small change occurring between the FEV_1 and expiration films. The diaphragms rise evenly, and the lungs become evenly opaque. The mediastinal structures remain in the midline (Figure 1). Care must be taken to ensure that the subject exhales to maximum vital capacity while the films are being taken. The spirographic record obtained simul-

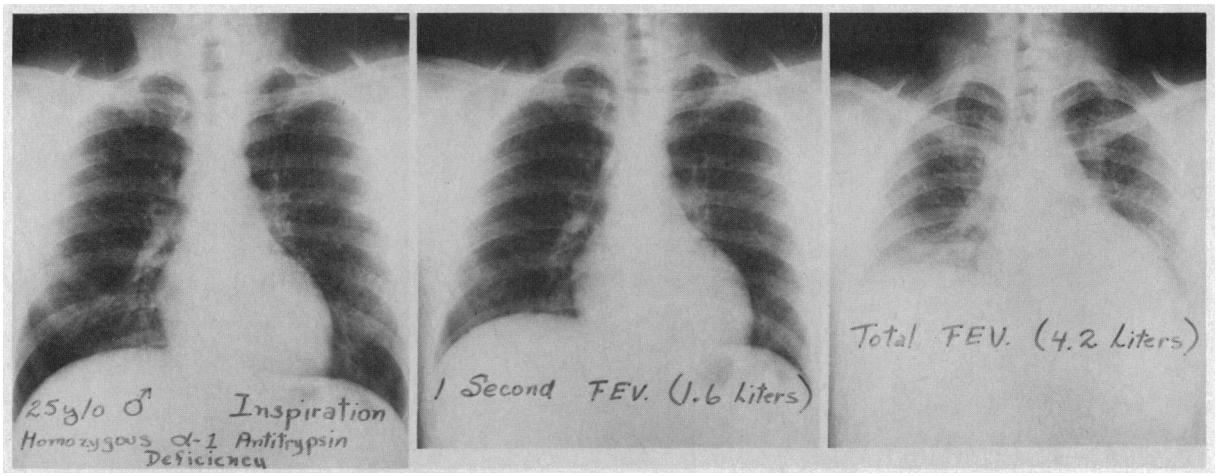

Figure 3.—Timed expiratory chest films of a 25-year-old man with diffuse obstructive airway disease associated with homozygous alpha-1-antitrypsin deficiency. The inspiration film is essentially normal. The total vital capacity is within normal limits as well (4.2 liters). A simple inspiration and expiration film on this patient would not reveal an abnormality; however, the FEV_1 film shows poor diaphragmatic motion compared with the inspiration film, and only 1.6 liters of air have been expired. No evidence of localized air trapping is seen.

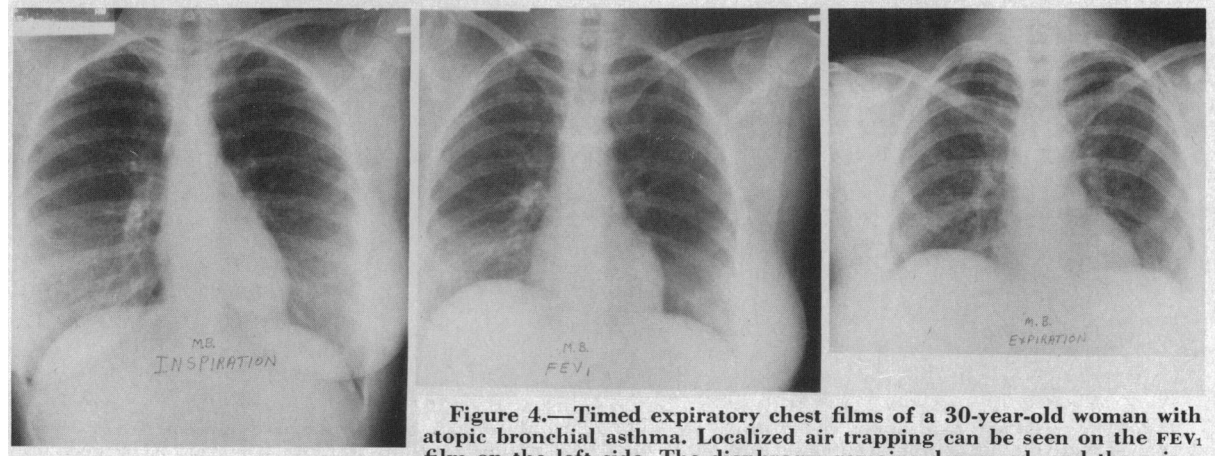

Figure 4.—Timed expiratory chest films of a 30-year-old woman with atopic bronchial asthma. Localized air trapping can be seen on the FEV_1 film on the left side. The diaphragm remains depressed, and there is a slight shift on the mediastinum to the right side. The left lung remains lucent, particularly in its lower portion. The full expiration and the inspiration films are normal, and the patient's spirographic tracings are also normal.

taneously with the x-ray exposures is compared with the control spirographic record obtained prior to the actual examination. Three false-positive readings, suggesting obstructive disease, resulted from lack of a full expiratory effort by the patient during the film exposure; these were easily detected by comparison with the spirographic records.

Restrictive disease is detected by diminished excursion of the diaphragms (Figure 2). As in the normal subject, the majority of diaphragmatic movement occurs between the inspiration and the FEV_1 films; however, the total movement is diminished.

Diffuse obstructive airway disease is manifested by less motion between the inspiration and FEV_1 films and more diaphragmatic elevation and decrease in size of the chest between the FEV_1 and the full expiration roentgenograms (Figure 3). If the increased airways resistance involves the lung fields in a relatively even fashion, symmetry of the diaphragms and the midline position of the mediastinum are maintained.

Localized trapping of air is easy to detect by this method and may occur in the presence of a normal vital capacity and FEV_1. If the trapping is marked, it will manifest itself by a retention of lucency in the zone of trapping on the FEV_1 film and the full expiration films. Frequently there will be diminished or lack of motion of one dia-

phragm and shift in the mediastinum away from the involved area. If, however, the trapping of air is incomplete, it may only be apparent on the FEV_1 film, and the full inspiration and full expiration films may be normal (Figure 4). Thus, incomplete localized obstruction of airways can be detected by this method.

A large number of measurements are currently being made from the films and correlated with the spirographic tracings and with determinations of lung volumes obtained by physiologic measurements. In addition, planimetric determinations of lung volumes from the films[8] are being correlated with plethysmographic determinations of lung volume. The number of measurements made thus far is not large enough to present at this time.

We think that this timed expiratory technique holds promise of being a simple and practical method that will enable radiologists to detect obstructive pulmonary disease at a considerably earlier stage than is currently possible. They should also be able to detect restrictive disease, and complete and incomplete localized zones of air trapping. We hope that analysis of various measurements made from the films and comparison of those to measured lung volumes will permit radiologists to make an estimate from the roentgenograms of lung volumes at full inspiratory capacity, FEV_1 and residual volume.

I will now ask Dr. Warren Gold to discuss the early diagnosis of chronic obstructive lung disease by physiologic techniques.

DR. GOLD:‡ For the last ten to fifteen years, pulmonary physiologists have spent many hours applying sophisticated physiologic tests to the evaluation of patients with severe end-stage obstructive lung disease. This approach is analogous to trying to determine the particular pathogenic pathway by which Bright's disease of the kidney develops. In fact, the study of end-stage pulmonary disease has provided very little information about the particular pathway by which the lung is finally destroyed. Our concern, as Dr. Murray indicated in his introduction, has been with the use of sophisticated techniques of physiologic evaluation of the lungs that may be abnormal in the face of unsuspected chronic pulmonary disease. Furthermore, we have been

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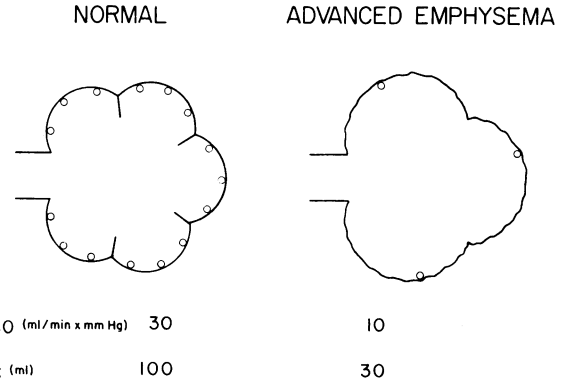

Figure 5.—Schematic models of the single breath carbon monoxide diffusing capacity (DCO) and the pulmonary capillary blood volume (VC) in the normal lung and in the advanced stage of emphysema. In the normal lung the alveoli are clustered about an alveolar duct leading into an airway; the open circles represent patent pulmonary capillaries. The lung of a patient with advanced emphysema is characterized by a decrease in the number of pulmonary capillaries, disruption of the normal architecture with a decrease in the number of alveoli, and an increase in the size of the remaining alveoli. Representative values for DCO and VC are shown for each of these conditions in the lower half of the figure.

concerned with the development of physiologic methods to differentiate the different types of diseases now lumped in the single clinical classification of chronic obstructive pulmonary disease. Figure 5 illustrates a model of the lung that we have found useful in the analysis of the abnormalities of structure and function of patients with emphysema. On the left is the normal arrangement of alveoli clustered about an alveolar duct leading into an airway. On the right are illustrated the destructive changes that develop in the case of advanced emphysema: The number of patent pulmonary capillaries is decreased, the number of alveoli is decreased, and the architectural framework is destroyed resulting in air spaces of abnormally large size with a decrease in elastic recoil properties. All of these features of emphysematous lungs have been described previously by pathologists.

Physiologically, these abnormalities would result in a decrease in the capacity of the lung to transfer gas from air spaces to the remaining pulmonary capillaries. In the laboratory we can measure the capacity of the lung to transfer a test gas (carbon monoxide) from the air spaces to the pulmonary capillaries.[9] Furthermore, we can subdivide this total capacity ($D_{L_{CO}}$) and actually measure the volume of blood contained in the pulmonary capillaries. If, in emphysema,

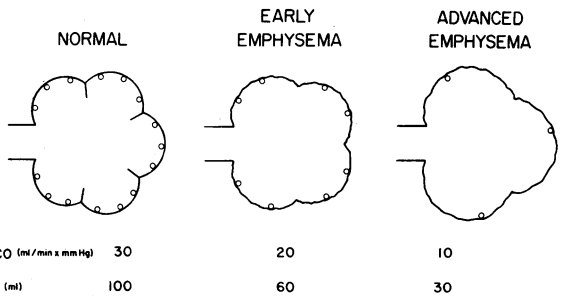

Figure 6.—Schematic models of the single breath carbon monoxide diffusing capacity (DCO) and the pulmonary capillary blood volume (VC) in the early and advanced stages of emphysema (see Figure 5). Representative values for DCO and VC are shown for each of these conditions in the lower half of the figure.

there is a decrease in the pulmonary capillary bed, then there will not only be a decrease in the $D_{L_{CO}}$, but also a decrease in pulmonary capillary blood volume (Vc) (Figure 5). These tests can be carried out in the laboratory rapidly, simply, and painlessly without needles or catheters and without discomfort to the patient. However, we are concerned with detecting abnormalities in asymptomatic patients with emphysema. Figure 6 illustrates the abnormalities to be expected in the lungs of a patient with early, less-severe emphysema. Even in this situation, we would postulate that the alveolar capillary surface would be reduced, resulting in a decrease in $D_{L_{CO}}$ and Vc.[10-13]

The second major feature of the emphysematous lung is a loss of elastic recoil. One can think of lung parenchyma as behaving as if it were composed of a set of springs that resist stretching. As lung volume is increased, increasing pressure is generated by the parenchyma to cause the lung to recoil to its residual volume. If the increase in lung volume continues, an increased elastic recoil pressure will be generated. The relationship between elastic recoil pressure and lung volume is illustrated in Figure 7. In contrast to the normal lung, the emphysematous lung has a set of "sprung" springs. The lung does not resist attempts to distend it with the same recoil pressure as the normal lung. This abnormality results in a shift in the elastic recoil curve to the left of the normal curve illustrated by the dashed line in the figure. This curve shows that the elastic recoil pressure is decreased at every lung volume while the slope of the pressure-volume curve is increased. The slope of the recoil curve, or lung compliance, is defined by

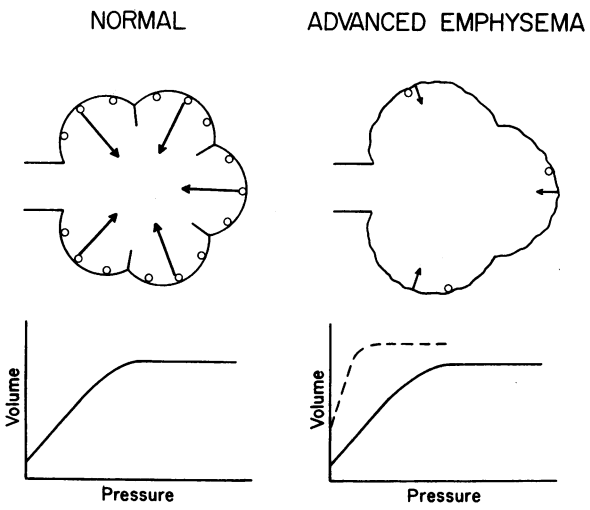

Figure 7.—Schematic models of lung elastic recoil in the normal lung and in the advanced stage of emphysema. The arrows represent the elastic recoil pressure generated by the lung, and the length of the arrow is proportional to the recoil pressure generated. Elastic recoil curves for each model are shown in the lower half of the figure. (Ordinate = lung volume; abscissa = elastic recoil pressure; solid line = normal lung; dashed line = advanced emphysema.)

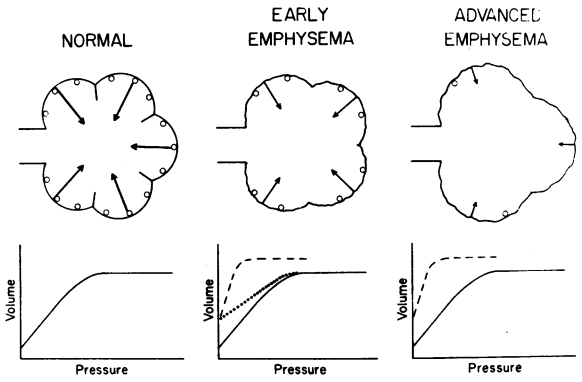

Figure 8.—Schematic models of lung elastic recoil in the early and advanced stages of emphysema. Elastic recoil curves for each of these models are depicted in the lower half of the figure. (Dotted line = early emphysema; see Figure 7 for explanation of other symbols.)

the change in lung volume divided by the change in recoil pressure. Lung compliance is a measure of lung distensibility, and as the recoil characteristics of the lung decrease, distensibility increases in patients with emphysema.

Figure 8 illustrates the changes in the elastic recoil behavior of the lung at an earlier stage of development of the emphysematous lesion. The elastic recoil curve of a lung with early emphysema might be represented by a composite of a normal curve representing normal regions of

lung and an abnormal curve representing the emphysematous regions of the lung. Consider the behavior of such a lung as it is inflated from residual volume to total lung capacity: With the application of a small pressure (for example, 5 cm H_2O), almost all of the emphysematous regions of the lung would inflate completely, but very little volume change would occur in the normal regions of the lung. In fact the normal regions of the lung would not become fully inflated until a pressure of 20 or even 50 cm H_2O had been applied. As indicated by the dotted line in Figure 8, at low lung volumes the curve reflects the emphysematous regions with a loss of recoil pressure, whereas at high lung volumes the curve reflects the more normal regions of the lung that have recoil characteristics closer to the normal range.[14-16]

On the basis of our knowledge of the pathologic changes in emphysematous lung, it appears that two types of tests would be useful in evaluating patients with this disease: (1) the transfer capacity for carbon monoxide ($D_{L_{CO}}$) and (2) the lung elastic recoil curve. To measure lung elastic recoil, however, we must approximate pleural pressure with an esophageal balloon. To avoid the minor discomfort associated with swallowing the esophageal balloon, we have tried to develop other less uncomfortable methods. One alternative approach is based on the fact that a large portion of the airways as well as the parenchyma of the lung are contained within the thorax, as indicated in Figure 9. These intrathoracic airways are subjected to the same distending pressure in the pleural space as the lung parenchyma. When there is a loss of lung elastic recoil, as in patients with emphysema, the negative pressure in the pleural space at a given lung volume is less than in the normal chest. As a result, the intrathoracic airways are subjected to a smaller distending pressure and, consequently, the airways of the emphysematous lung are narrower than those of a normal lung at the same volume. This change in airway geometry results in a pronounced increase in airway resistance since resistance is inversely proportional to the fourth power of the radius.

We have taken advantage of the effect of loss of lung elastic recoil on airway resistance by measuring the resistance to airflow at different lung volumes using a body plethysmograph. The relationships are illustrated in Chart 2. Normally, airway resistance does not change greatly from total lung capacity to functional residual capacity, but from functional residual capacity to residual volume the resistance increases considerably. We believe this increase in resistance reflects the fact that residual volume is determined by airway closure. Therefore, the nearer the patient breathes to his residual volume, the more the airways are narrowed and the greater the increase in airway resistance. In a lung with a loss of elastic recoil, the diminished support of the intrathoracic airways causes the airways to narrow prematurely at a relatively large lung volume; concurrently, airway resistance increases prematurely as lung volume decreases.

Since a patient with early emphysema has an abnormal elastic recoil curve at low lung vol-

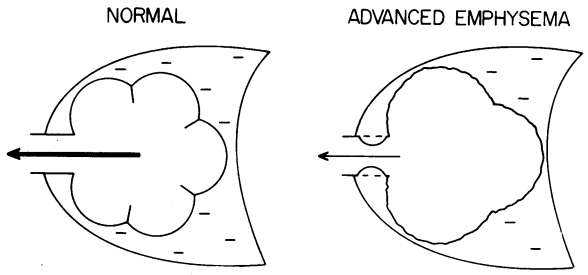

Figure 9.—Schematic models of the effect of loss of lung elastic recoil on airway geometry. The model of a normal lung shows the alveoli clustered around the alveolar duct communicating with an airway and contained within the chest wall. The pressure inside the chest but outside the lung (pleural pressure) is negative (shown by — symbols in pleural space), and acts not only to distend the parenchyma but to dilate the intrathoracic airways. The model of advanced emphysema illustrates a relatively less negative pleural pressure at the same lung volume. This results in less support for the intrathoracic airways leading to airway narrowing. The result is a decreased flow (decreased arrow in the airway) because of an increase in airway resistance.

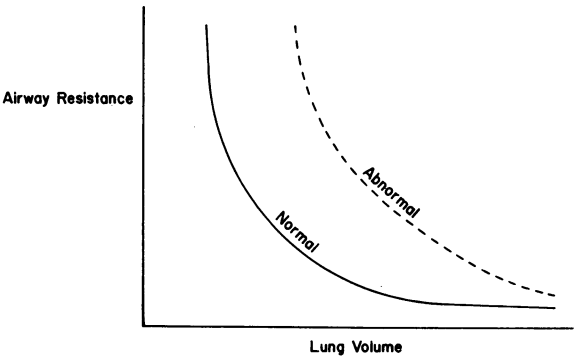

Chart 2.—Relationship between airway resistance and lung volume. Total lung capacity is at the right of the volume axis, residual volume at the left of the volume axis. (Solid line = normal lung; dashed line = abnormal or emphysematous lung.)

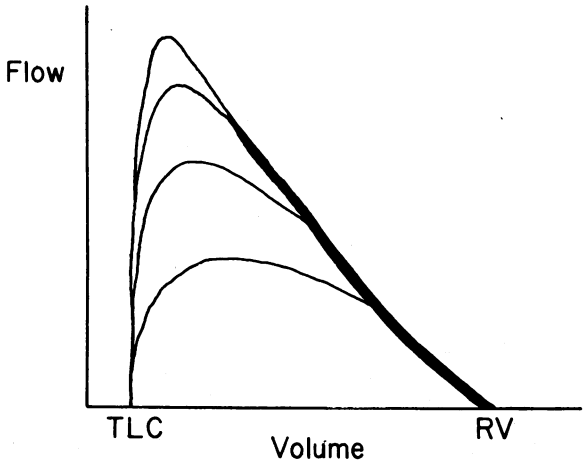

Chart 3.—Relationship between maximal expiratory flow and lung volume. The series of four curves, which start at total lung capacity (TLC) and end at residual volume (RV), represent repeated measurements of flow-volume curves with progressively increasing effort in one normal subject.

umes only, we predict that the resistance-volume curve is abnormal primarily at low lung volumes; in fact, the airway resistance might be perfectly normal at functional residual capacity or any higher lung volume. Although this measurement is easier to perform than that of lung elastic recoil, it does require cooperation on the part of the patient. Many patients with obstructive airway disease find it particularly difficult to breathe at low lung volumes when airflow resistance is greatly increased. We therefore examined other methods that would be more comfortable but would yield information reflecting the loss of elastic recoil properties.

In our laboratory, the best screening procedure to evaluate the mechanical properties of the lung is to measure the relationship between maximal expiratory airflow and lung volume (flow-volume curve).[17,18] There are a number of spirometers on the market at present that provide a signal representing expired volume as well as another signal representing the flow rate at which the gas leaves the lung and enters the spirometer. These relationships can also be measured by a body plethysmograph, but this requires more technicians and money. In measuring flow-volume curves, the patient takes a deep breath to total lung capacity and breathes out while flow and volume are recorded. The maneuver is then repeated with still greater effort until finally the patient exhales with as much effort as possible as illustrated in Chart 3.

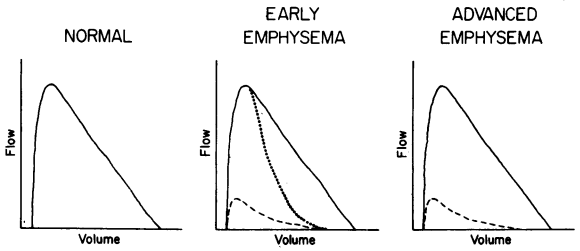

Chart 4.—Representative flow-volume curves in normal subjects and in patients with early and advanced stages of emphysema. (Solid line = normal lung; dashed line = advanced emphysema; dotted line = early emphysema.)

The resulting outer envelope of this series of curves defines the maximal expiratory air flow that can be generated at any particular lung volume. There are a number of important features of this curve: During the first 20 percent of the expired volume, the maximal air flow rate is dependent on the effort generated by the subject. This means that during exhalation of the first 20 percent of the total expired volume, the harder the subject tries, the greater the flow rate he achieves. Once he has exhaled the first 20 percent of the vital capacity, however, the flow rate during the remaining portion of the vital capacity is effort *independent*. This is indicated by the fact that all of the curves converge to form the heavy envelope in Chart 3.

Two variables determine this flow-volume envelope: (1) Maximal flow rate at a given lung volume is directly proportional to the elastic recoil pressure generated by the lung at that lung volume. If there is a loss in elastic recoil, there is a reduction in the maximal expiratory flow rate. (2) Maximal expiratory flow also depends on airway geometry. If the airways are abnormally narrow, then there is a reduction in the maximal respiratory flow rate. In patients with emphysema, these two variables are interrelated: The loss of lung elastic recoil not only decreases the driving pressure producing flow at a given lung volume, but also alters airway geometry so that flow is reduced because the airways are narrowed. Chart 4 illustrates the changes expected in the flow-volume curve in patients with advanced emphysema and in other patients with early emphysema. In the advanced stage of the disease, the decided loss in lung elastic recoil at all lung volumes greatly decreases the driving pressure and narrows the airways, resulting in a decrease in maximal expiratory flow rates at all lung volumes.

TABLE 1.—*Results of Preoperative Pulmonary Function Studies in a 52-Year-Old Man*

Pulmonary Function Study	*Predicted*	*Observed*
Lung Volumes		
Vital Capacity (L)	4.7	5.1
Total Lung Capacity (L)	7.1	7.1
Residual Volume (L)	2.4	2.5
Lung Mechanics		
Forced Expiratory Volume, 1 sec (L)	>3.3	3.3
Maximal Expiratory Flow Rate (L/min)	350-500	330
Airway Resistance (cm H_2O/L/sec)	0.7-1.8	1.4
Diffusion		
$D_{L_{CO}}$ (ml/min/mm Hg)	34	15.4

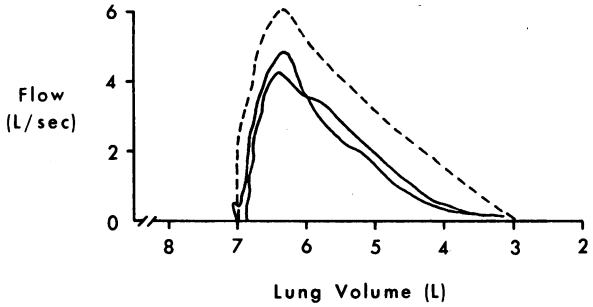

Chart 5.—Maximal expiratory flow-lung volume curve in a patient with clinically unsuspected emphysema. (Solid line = patient with unsuspected emphysema; dashed line = curve obtained in a healthy man of comparable age.)

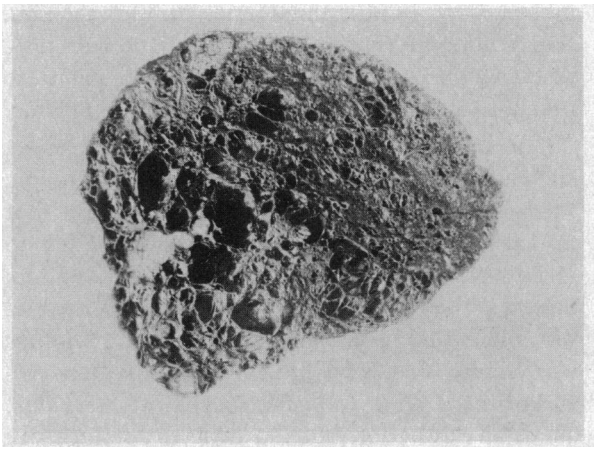

Figure 10.—Right upper lobe resected from patient with clinically unsuspected emphysema (mid-left). This is a cut section through a formalin-fixed lobe inflated with 25 cm of water pressure.

At an earlier stage of this disease, the changes in the flow-volume curves would be slightly more complex: At high lung volumes, where the recoil characteristics of the lung are virtually normal, driving pressure and airway geometry would be normal so the maximal flow rates generated would probably be within the normal range. At low lung volumes, on the other hand, when the elastic recoil is decreased, maximal expiratory flow would be decreased owing to both the reduction in driving pressure and the narrowing of the airways.

Let me apply this theory to a clinical problem. A 52-year-old carpenter was referred to the hospital last year because of low back pain. He had smoked one package of cigarettes daily for 20 years but denied respiratory symptoms. A chest roentgenogram revealed a nodule in the upper lobe of the right lung. Preoperative pulmonary function studies are shown in Table 1. The normal vital and total lung capacities ruled out a restrictive pulmonary defect. The normal FEV_1, maximal expiratory flow rates, and airway resistance suggested that he did not have airway obstruction. The striking abnormality in these screening studies was the pronounced decrease in $D_{L_{CO}}$. There are two possible causes for such an abnormality: (1) vascular disease involving the microcirculation of the lung, or (2) emphysema with destruction of the pulmonary capillary bed.

We were able to differentiate these two possibilities by examining the flow-volume curve shown in Chart 5. The flow-volume curve obtained in the patient is compared with that of a healthy man of the same age with a comparable lung volume. Although there was a slight reduction in peak flow rate at total lung capacity, the patient was able to generate a peak flow rate of 5 liters per second (or 300 liters per minute), which is practically normal for a man of his age. The striking abnormality in the patient's flow-volume curve occurred at a low lung volume: the absolute flow rate was decreased and the curve became qualitatively different from the normal curve. Instead of flow decreasing linearly with volume, the curve became concave upwards. On the basis of the decrease in $D_{L_{CO}}$ and the abnormal flow-volume curve, we predicted that when the lobe was resected the pathologist would find emphysema. Figure 10 shows a cut section through the formalin-fixed inflated lobe, revealing severe emphysema throughout the specimen.

Not only can physiologic studies detect the presence of emphysema when it is clinically un-

suspected, but physiologic studies can differentiate different kinds of obstructive airway disease. In a group of patients with "chronic bronchitis" Macklem's group found obliterative bronchitis involving small airways of 2 mm in diameter or less.[19] In the human lung, the peripheral airways of 2 mm in diameter may be the only site of pathologic change. In this kind of peripheral airway disease, the small airways may be virtually completely obstructed, yet careful anatomic studies of inflated lungs from such patients reveal that the regions of lung distal to the obstructing lesion are ventilated and not atelectatic.[20] These anatomic studies indicate that collateral ventilation to the region of lung distal to the site of obstruction is sufficient to maintain normal expansion of the parenchyma.

The problem then is to determine what effect such a lesion would have on pulmonary function. Morphometric studies by Weibel suggest that approximately 90 percent of the resistance to airflow resides in airways larger than these 2 mm airways.[21] Physiologic studies by Macklem and his colleagues[22] confirmed the anatomic findings of Weibel. As Mead indicated in a recent editorial in the *New England Journal of Medicine,* small airways contribute so little to total airway resistance that substantial decreases in cross sectional area of these airways could occur in this kind of disease with only small and perhaps even undetectable influence on total airway resistance.[23] Hence, the usual tests of pulmonary function could be normal. Macklem and Mead demonstrated that despite the small contribution of such small airways to total airway resistance, the patency of small airways has a critical effect on the distribution of volume within the lung.[22] For example, if 50 percent of the bronchi at the 2 mm level were obstructed, total airway resistance might increase only five percent, but lung distensibility or compliance would be halved. Following this suggestion, Woolcock and coworkers studied a group of patients with bronchitis and found a change in lung distensibility.[24] In addition, they observed that the effect on lung compliance could be magnified by more rapid breathing—that is, with increasing respiratory frequency, lung compliance decreased (Chart 6.)

The basis for this observation is illustrated in Figure 11. In this model, the intrinsic elastic properties of the lung units are equal, but the airway to one of the units is narrowed. Under

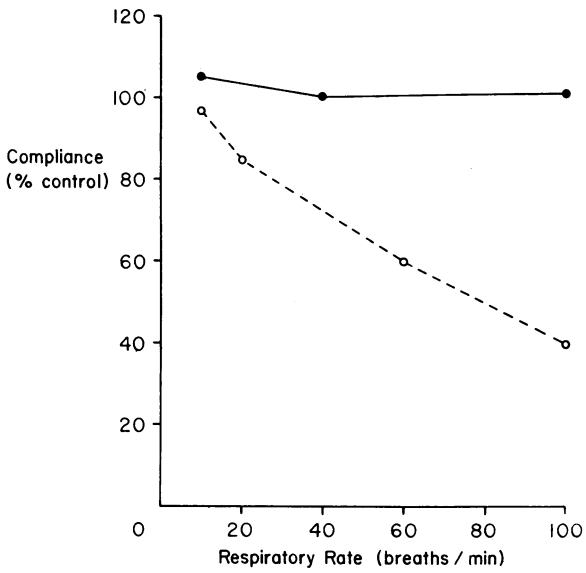

Chart 6.—The effect of respiratory rate on lung compliance. The solid line shows the effect of increasing respiratory rate in a healthy subject and indicates that lung compliance in healthy subjects is relatively independent of increasing respiratory rate. In contrast, the dashed line shows the results in a patient with peripheral airway disease and indicates that the lung compliance decreases decidedly with increasing respiratory rate in this condition.

dynamic conditions, the tidal ventilation passes preferentially to the unit with the patent airway. As the respiratory rate increases, this tendency increases, but as the rate increases, a greater fraction of the driving pressure dissipates in overcoming the resistance to airflow, leaving a decreasing pressure available to inflate the lung units. Thus, as the respiratory rate increases, the volume change produced by the inflating pressure diminishes and the dynamic lung compliance decreases. Since this lesion does not affect the lung parenchyma, the D_{Lco} and static lung elastic recoil remain normal.

Table 2 summarizes the physiologic differences between emphysema and peripheral airway disease. In early stages of emphysema, there is a decrease in diffusing capacity and pulmonary capillary blood volume associated with a loss of lung elastic recoil, particularly at low lung volumes. This results in an increase in airway resistance and a decrease in maximal air flow rates, particularly at low lung volumes. The two screening studies that are most useful in making this diagnosis are the D_{Lco} and the flow-volume curve. The physiologic diagnosis of peripheral airway disease is based on the following criteria: The D_{Lco}, the pulmonary capillary blood vol-

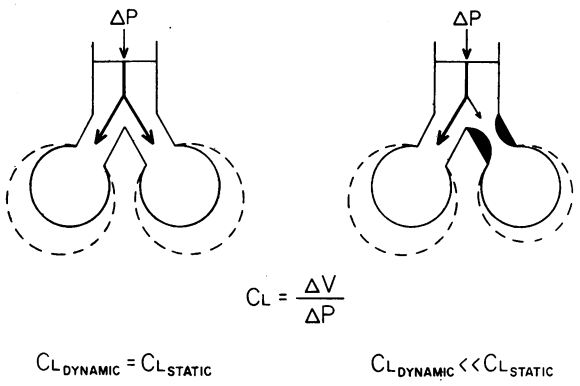

Figure 11.—Effect of peripheral airway obstruction on dynamic lung compliance. The effect of inflating the lung with a fixed, driving pressure (ΔP) is illustrated in a normal lung (left) and in a lung with peripheral airway disease (right). In the normal lung, the change in volume (dashed lines) produced by a change in transpulmonary pressure is similar under static and dynamic conditions up to respiratory rates of about 100 breaths per minute. In peripheral airway disease, although the intrinsic elastic recoil properties of the lung units are normal and equal, the airway to one of these units is narrowed. Under static conditions, the change in lung volume would be independent of the pressure of the airway obstruction, but under dynamic conditions, the tidal ventilation passes preferentially to the unit with the patent airway. As the respiratory rate is increased, a greater fraction of the driving pressure (ΔP) will be dissipated in overcoming the resistance to air flow, leaving a decreasing pressure available to inflate the lung units. Thus as respiratory rate increases, the volume change (dashed lines) produced by the inflating pressure diminishes and the dynamic lung compliance decreases. The amount of air flow entering the air space is indicated by the size of the arrow within the airways.

ume, and the static elastic recoil curves are normal, but the dynamic compliance decreases during rapid breathing.

Thus, physiologic tests of pulmonary function can be used to detect obstructive pulmonary disease when it is clinically unsuspected and, in addition, these tests may be useful in differentiating different types of chronic obstructive pulmonary disease.

At this point I would like to turn the session over to Dr. Allen Cohen, who is going to try to take us to an even earlier point in the obstructive pulmonary diseases by discussing recent biochemical advances concerning the diagnosis and clinical significance of alpha-1-antitrypsin.

DR. COHEN:§ Alpha-1-antitrypsin (ALT) deficiency is the only biochemically defined genetic defect that has definitely been related to emphysema. For this reason, ALT deficiency has been the subject of a great deal of research and controversy. Some of this controversy has made the literature difficult to interpret and one's own laboratory tests difficult to evaluate.

§Allen B. Cohen, M.D., Assistant Professor of Medicine, University of California, San Francisco; Director of Respiratory Intensive Care Unit, San Francisco General Hospital.

TABLE 2.—*Summary of Physiologic Differences between Emphysema and Peripheral Airway Disease*

Early Emphysema	*Peripheral Airway Disease*
	Normal
↓$D_{L\,CO}$ and pulmonary capillary blood volume	$D_{L\,CO}$ and pulmonary capillary blood volume
At low lung volume	Normal elastic recoil (static)
↓elastic recoil (static)	↓Compliance (dynamic)
↑resistance	
↓maximal flow rates	

Alpha-1-antitrypsin is an alpha-1-globulin, which means that it migrates between albumin and alpha-2-globulin in routine electrophoresis of serum proteins. It has a molecular weight of 58,000 and is similar in many respects to albumin; however, it has a unique feature that has been of great interest to investigators in this area: it inhibits proteolytic enzymes. Alpha-1 is an appropriate name for this protein but antitrypsin is not. Trypsin is only one of many enzymes inhibited by ALT. Some of the many other proteolytic enzymes inhibited by ALT are elastase, chymotrypsin and leukocyte fibrinolytic enzymes.

The relevance of ALT to clinical disease is controversial. Eriksson,[25] the investigator who described ALT deficiency, studied a large population in Sweden, where such investigations are possible because of the relative immobility of the people. In a random sample of the population he found an incidence of approximately 0.05 percent for the homozygous disease state. The presence of the heterozygous gene was diagnosed by an intermediate level of ALT half way between normal and homozygous. He found a 4.7 percent incidence of the heterozygous gene. This study is unassailable in terms of demographic design and application of demographic mathematics. However, some of the more sophisticated techniques of physiologic assessment of lung function and evaluation of the phenotypes of ALT deficiency were not available to Eriksson at that time. Since then, Kueppers, Fallat and Larson[26] and Lieberman, Mittman and Schneider[27] have applied newer techniques of assessing pulmonary

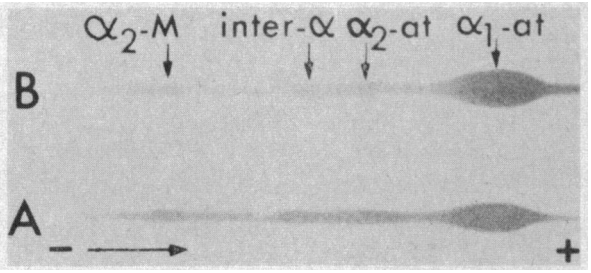

Figure 12.—Fibrin agar electrophoresis of serum from a heterozygote for the common α_1-antitrypsin gene before (A) and 3 days after the injection of typhoid-paratyphoid vaccine (B). The dark areas indicate where the fibrin has remained undigested by trypsin due to the presence of trypsin-inhibitors in the different electrophoretic regions. (α_2-M = α_2-macroglobulin, inter-α = inter-α-trypsin inhibitor, α_2-at = α_2-antitrypsin, α_1-at = α_1-antitrypsin.) Note the large zone of inhibition due to increase of α_1-antitrypsin in B, whereas the size of the zones of inhibition due to the other inhibitors has remained unchanged. (From Kueppers[28])

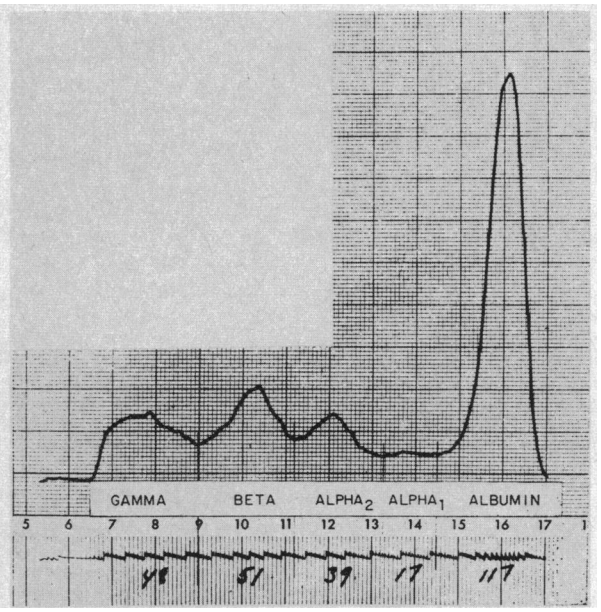

Figure 13.—Paper electrophoresis of serum proteins. Absence of α_1-globulin peak in homozygous α_1-antitrypsin deficiency, with a spuriously normal quantitative measurement of the α_1-globulin is seen. Protein values were as follows: total, 7.3; albumin, 3.14; α_1-globulin, 0.460; α_2-globulin 1.044; β-globulin 1.365; and γ-globulin, 1.292 gm/100 ml. (From Lieberman, Mittman, and Schneider[27])

function to patient populations in Northern and Southern California and have come to different conclusions. Kueppers et al[26] used crossed gel electrophoresis, which will be discussed later, and found that approximately 25 percent of the patients with obstructive lung disease had either heterozygous or homozygous ALT deficiency, whereas Lieberman et al[27] concluded that patients under the age of 40 years with emphysema have approximately a 50 percent incidence of ALT deficiency. These studies have a problem, too, because the investigators were unable to carry out the kind of large scale demographic study that was possible in Sweden. In the Swedish studies there was no increase in the incidence of emphysema in patients with the heterozygous state. I think each of the studies has certain problems built into it, and that the relationship between the heterozygous state and emphysema has to be considered an open question.

There are several laboratory methods for evaluating ALT. The first one I will mention, which is used by Kueppers,[28] is not useful diagnostically, but is helpful in understanding the trypsin or fibrinolytic inhibitory capacity of human serum; Figue 12 shows the different serum proteins that inhibit fibrinolytic enzymes.[28] Fibrinogen in an agar gel is put on a microscope slide. Trypsin is added to the gel and when the fibrinogen is digested, the gel becomes translucent. Serum is electrophoresed in a separate starch gel, and this gel is laid on top of the fibrin-agar gel. The separated serum components diffuse into the fibrin-agar gel. Trypsin is then added to the fibrinogen gel and the gel clears everywhere except in the area containing the inhibitors from serum. Therefore, the dark areas represent those serum proteins that inhibit trypsin. In normal human serum ALT contributes most of the antitryptic activity, but at least four other antitrypsins are also present.

The diagnostically useful tests for ALT deficiency can be divided into three major categories. One category measures by simple serum electrophoresis the entire class of proteins to which ALT belongs. The second category measures the specific protein ALT either quantitatively or qualitatively. The qualitative test is the best way to diagnose the heterozygous state at the present time. The third category measures the function of the protein.

Serum protein electrophoresis is the most widely available test (Figure 13).[27] Albumin migrates farthest, then ALT; gamma globulin is at the anodal end. The ALT is represented on the electrophoretic pattern by a peak that is a little bit smaller than alpha-2 but the alpha-1 peak is absent in sera from a patient with a homozygous deficiency of ALT. Fallat* has pointed out (per-

*Robert Fallat, M.D., Chief, Chest Diseases, Pacific Medical Center, San Francisco.

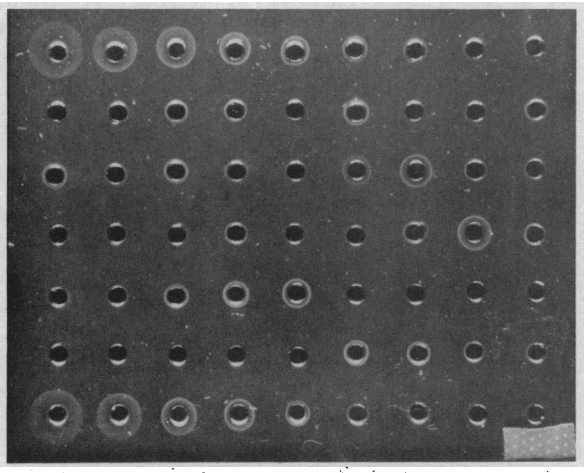

Figure 14.—Quantification of alpha-1-antitrypsin by radial diffusion. Serial dilutions of the standard were added to the top and bottom rows of holes. Concentration of alpha-1-antitrypsin is proportional to the log of the radius.

sonal communication) that it is well worth while to look at the electrophoretic pattern yourself because if the baseline is not set exactly right, a normal level of A1T can be reported even when the A1T peak is absent. Lieberman and associates[27] reported that you can also diagnose the heterozygous patient with this method, but better techniques are available.

Figure 14 depicts a method that is employed currently for quantifying the amount of A1T in serum. An aliquot of melted agar is cooled to a temperature that will not destroy antibodies; antibodies specific for A1T are then mixed into it. The agar is then poured onto a glass plate and holes are cut in the agar. A standard serum with a known concentration of A1T is diluted serially. The diameter of the precipitin disk is compared with the concentration and the standard curve is drawn; the diameter of the unknown disk is then used to calculate the concentration of A1T. The biggest problem with this technique is the requirement for standards of known A1T concentration. The laboratory must start the assay with purified A1T in order to have an appropriate standard. With the purified standard, one can make other standards that do not have to be pure. The problem is the purification of A1T. Kueppers was able to purify A1T while he was at the University of California in San Francisco, so there are reasonable standards in some of the local laboratories. Reports of studies in which this technique was employed must state exactly how the standards were derived; standards acquired from commercial laboratories cannot always be relied upon.

The cross gel electrophoresis is also based on detecting the A1T specifically, and it also uses an antibody to A1T. Normal serum is electrophoresed in starch gel. The gel containing the electrophoresed serum is then cut out and placed on a plate similar to the one discussed earlier, only the agar has antibodies in it. Then the electrophoresed serum is reelectrophoresed into the agar. The precipitates that form in the gel are characteristic of different phenotypes of A1T (Figure 15).[29] The phenotypes of A1T act as codominant alleles. There is only 1 locus for the A1T gene, but it seems to control a complicated pattern demonstrated on the cross gel electrophoresis. In more recent work, Fagerhol and Laurell[30] found that there are many more bands on the crossed gel electrophoresis than were previously described. The important phenotypes are shown in the top row of Figure 15. The MM phenotype is the one most commonly seen, and the others are standardized by this third peak. The other peaks are standardized by the location of this peak. The FF phenotype migrates faster in the electrical field. This property gives this phenotype its name. The ss is a slow variant in this phenotype. The major band is slower than the major band in the MM phenotype. zz is the homozygous deficient phenotype, and the other patterns shown in Figure 15 occur in different kinds of heterozygous A1T deficiency states. Crossed gel electrophoresis is quite complex, but it has certain advantages over the other methods and is the only way to diagnose a patient's A1T phenotype.

The trypsin activity is then tested to see how much of it has been inhibited. In the radial diffusion technique, the standard deviations are broad and the heterozygote and normal phenotypes may be difficult to differentiate. Both the trypsin inhibitory capacity and the radial diffusion tests are less than perfect methods of diagnosing heterozygotes, but because of their simplicity they are the main tests in current use. Another problem with the trypsin inhibitory capacity is that A1T is only one of the proteins in human serum that inhibits trypsin. The test is still reasonably good because A1T makes up 90 percent of the normal trypsin inhibitory capacity of the human serum. Another major problem in using either the trypsin inhibitory capacity or the

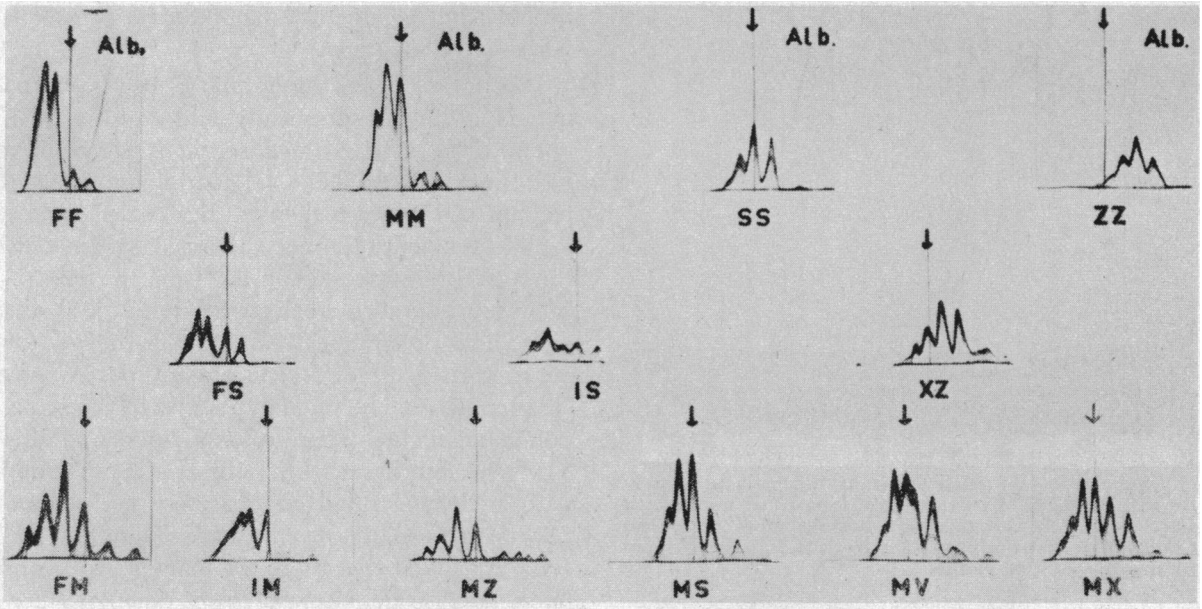

Figure 15.—The immunoprecipitation pattern after antigen-antibody crossed electrophoresis of sera with different α_1-antitrypsin phenotypes. Initial separation is by discontinuous starch gel electrophoresis (pH 4.95). The antiserum in the agarose-contained anti-α_1-antitrypsin and antialbumin (upper series) or only anti-α_1-antitrypsin (middle and bottom series). The arrow above each vertical line marks the position of band 4 of phenotype MM. (From Fagerhol and Laurell[29])

quantitative A1T concentration tests, usually carried out by the radial diffusion method in diagnosing the heterozygous state, is illustrated by an interesting experiment performed by Kueppers (Chart 7).[28] A pyrogen, in this case parathyroid vaccine, was given to volunteers with homozygous, heterozygous, or normal genotypes for A1T. The level of A1T did not increase in the homozygous A1T-deficient patients under the stress of fever, but A1T increased to the normal range in the heterozygous patients. This means that the patient with bronchitis or emphysema who has an infection might have a normal trypsin inhibitory capacity and a normal level of A1T and yet be a heterozygote. For this reason crossed gel electrophoresis is currently the most reliable test for diagnosing the heterozygote. Certain other states, such as pregnancy, can also raise the heterozygous levels into the normal range.

In the San Francisco Bay Area both the trypsin inhibitory capacity and the radial diffusion quantitation tests are performed in the laboratory of Dr. H. H. Fudenberg at the University of California, San Francisco. The radial diffusion test is also performed in the laboratory of Dr. R. Fallat at the Pacific Medical Center, who is particularly interested in receiving serum specimens from physicians in the Bay Area. The cross gel electrophoresis test is being developed in both laboratories but it is not yet available to physicians for routine studies.

There are several clinical characteristics of the patient with A1T deficiency. The major clue is the familial incidence, although other forms of emphysema also have a familial incidence.[31] Another important clue is the onset of emphysema at a young age, since several studies indicate that people who have clinical emphysema by the age of 40 have a higher incidence of A1T deficiency than other emphysematous patients. In addition, the chest radiograph of a patient with emphysema due to A1T deficiency frequently shows evidence of a basilar distribution of bullous emphysema.

Finally, there are many current hypotheses as to the cause of emphysema in patients with low levels of A1T in their serum. Most hypotheses start with the relatively good assumption that the cause of emphysema is related to a function of A1T that we know about—that is that A1T inhibits proteolytic enzymes. The hypotheses are as many as there are investigators. Alpha-1-antitrypsin operates on both ends of the coagulation system and inhibits thrombin and plasmin, so a coagulation defect of some kind, such as pulmonary capillary occlusive disease, could perhaps

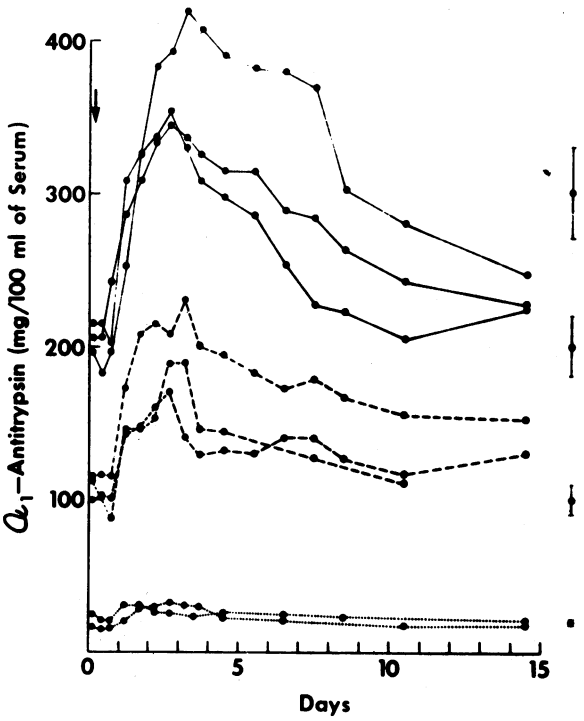

Chart 7.—Changes in α_1-antitrypsin levels of serum following the intravenous injection of 0.2 ml typhoid-paratyphoid vaccine (arrow) in the genetically different individuals. (Homozygotes for common gene = solid line, heterozygotes for α_1-at deficiency gene = dashed line, homozygotes for deficiency gene = dotted line.) (Standard error of the method is at the right.) (From Kueppers[28])

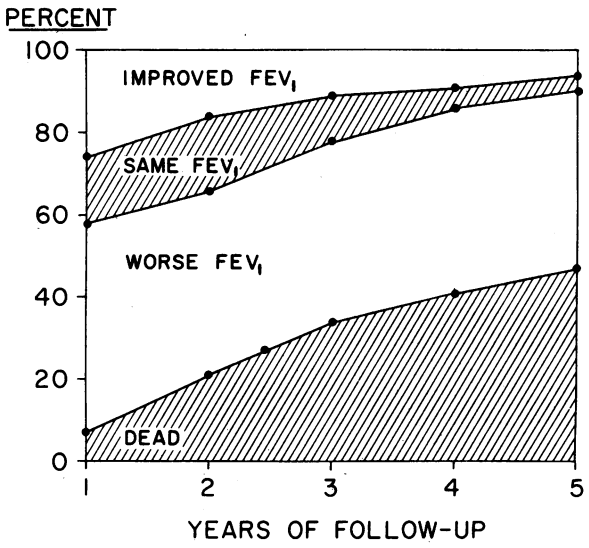

Chart 8.—Overall course of FEV_1 in 200 patients with obstructive lung disease. (From Burrows and Earle[33])

predispose to emphysema in these patients. Other investigators, Lieberman among them, have stressed the inhibition of fibrinolytic enzyme in leukocytes by ALT. Lieberman suggested that enzymes from the leukocytes are not inhibited in the lungs of these patients and therefore they digest lung tissue. Gross and coworkers[32] produced emphysema in experimental animals by injecting papain down the trachea; in just a few days an emphysema-like condition developed. The short time necessary to cause these changes makes this a poor model of emphysema, but it looks pathologically very much like the human disease. The predominant line of thinking is that some kind of proteolytic destruction occurs that the patient is unable to combat.

Dr. Murray will now deal with the most difficult parts of this discussion: What is the major advantage in making an early diagnosis, and what can one do for his patients once he has established the diagnosis?

DR. MURRAY: Even though we now move from the realm of science to the realm of speculation, it is crucial that we address ourselves to two questions that are inevitable corollaries to the efforts toward early diagnosis. First, what treatment can we offer either to the patient in whom emphysema or chronic bronchitis has been detected early, or to the patient who has a biochemical abnormality that we believe predisposes him to the development of these diseases? Second, and an even more crucial and difficult question to answer, what influence do therapeutic interventions have on the natural history of these diseases? We are able to offer recommendations for preventive measures based on very plausible assumptions about the pathogenesis of these diseases, but our state of knowledge at present is so incomplete that we are unable to document what effect these maneuvers have on the subsequent course of asthma, pulmonary emphysema, and chronic bronchitis.

Perhaps the best way to approach the problem is to examine what is known about the natural history of advanced lung disease. Chart 8 reproduces data from a prospective study by Burrows and Earle[33] of 200 patients with chronic obstructive lung disease who were observed for at least five years. During the period of observation, about 40 percent of the patients died and most of the remainder had a progressive worsening of their FEV_1, indicating an increase in severity of their obstructive airways disease. The criteria for inclusion of patients in the study were suffi-

TABLE 3.—*Data from Selected Studies Showing the Decline of Certain Pulmonary Function Variables in Patients with Obstructive Lung Disease and in Normal Subjects*

Study	*Test**	*Change (ml/year)*
Chronic obstructive lung disease		
Howard (34)	$FEV_{0.75}$	−83
Fletcher and Oldham (35)	VC	−79
Burrows and Earle (33)	VC	−86
	$FEV_{1.0}$	−56
Normal subjects		
Kory et al. (36)		
Men	VC	−22
	$FEV_{1.0}$	−28
Ferris et al. (37)		
Men	FVC	−25
	$FEV_{1.0}$	−27
Women	FVC	−23
	$FEV_{1.0}$	−22

*Abbreviations: VC = vital capacity; FVC = forced vital capacity; FEV = forced expiratory volume (subscript refers to time of measurement in seconds).

TABLE 4.—*General Categories of Treatment That Are Frequently Administered to Patients with Chronic Obstructive Lung Disease*

Category of Treatment and Methods
A. Prevent inflammation
1. Stop smoking
2. Treat infection
3. Avoid pollutants
B. Expectorants
1. Hydration
2. Pharmaceuticals
C. Bronchodilators
1. Catecholamines
2. Theophyllines
3. Steroids
4. Other
D. Ventilatory support
1. Oxygen
2. Mechanical ventilation
E. Rehabilitation

ciently rigid that only patients with advanced disease were enrolled; however, data on them are by no means unique, as is shown in Table 3 in which the results of somewhat similar studies by English investigators are presented.[34-36] In England the deterioration of FEV_1 per year was even greater than that observed in the United States study. All of these values are several times greater than the normal attrition of FEV_1 that occurs with age, as was documented by the large surveys of Kory et al[36] and Ferris et al.[37]

There were some interesting trends evident in the British studies that pertain to the question of prevention and therapy. Howard[34] observed that patients who smoke heavily have a greater worsening of their ventilatory capacity than those who have either stopped smoking or continued at a reduced rate. Similarly, he observed that the deterioration is accelerated in those patients who have more frequent respiratory infections as documented by the number of courses of antibiotics required in a given period. In a report to the British Medical Research Council Fletcher and Oldham[35] further evaluated antibiotics in patients with chronic bronchitis and found that antibiotics do not significantly reduce the number of intercurrent respiratory infections, but serve to reduce the number of days of disability from them. This finding is consistent with the current belief that intercurrent infections, which plague the life of patients with chronic obstructive lung disease, are initiated by nonbacterial agents (presumably viruses) but are then perpetuated and aggravated by secondary bacterial superinfection of the lower airways.

Table 4 lists the general categories of treatment that have been used for patients with chronic obstructive lung diseases. One must appreciate the difficulties in evaluating the influence of a single therapeutic approach when it is given to a group of patients with a disease that characteristically waxes and wanes who are usually treated with multiple remedies. But in all studies in which the effects of bronchodilators, expectorants, antibiotics, oxygen, and rehabilitation were examined, one uniformly finds that there is *never* an improvement in pulmonary function; in fact there is a steady reduction in FEV_1. The sad conclusion emerges that despite all known therapeutic interventions tried to date, nothing has been found that will retard, much less reverse, the relentless tendency for the obstruction of airways to increase.

On the brighter side, however, is the reasonably consistent subjective improvement felt by patients in various rehabilitation programs. The patients feel better, they have greater independence in their daily activities, and they seem to enjoy life more. Also, one can show an increase in their work capacity, which in view of the lack of change in pulmonary function is generally attributed to the effects of training and physical conditioning. Finally, one important benefit from

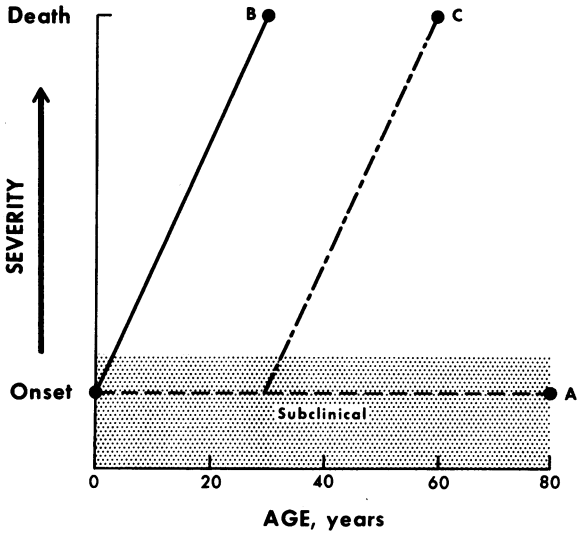

Chart 9.—A schematic representation of three possible clinical courses that a patient with a genetic abnormality could follow. (Line A = no detectable disease; line B = continuously progressive disease leading to death; and line C = disorder without clinical manifestations unless external factors are introduced.)

the various therapeutic interventions is that they keep the patient out of the hospital, so there is a definite socio-economic gain from treatment. It should be emphasized that the rather gloomy conclusions concerning the effects of treatment on pulmonary function were obtained in studies of patients with *advanced* pulmonary emphysema and bronchitis. The results of treatment in the patient with very early disease, or in those predisposed to the development of chronic obstructive lung disease, are unknown and will depend to a large extent on the mechanisms by which progressive loss of pulmonary function occurs.

Chart 9 shows some possible clinical courses that a person with a genetic abnormality might follow during the (possible) development of his disease. There are a number of permutations on the pathways that are shown, but the three indicated in the chart serve well as prototypes for discussion. The figure depicts the increasing severity of a given disease from its onset to the patient's death. The time scale is in years to represent an arbitrary selection of the duration of the illnesses. Line A indicates the subject who has a specific genetic abnormality but one which is completely harmless and not associated with clinically detectable disease. An example of this might be the person who has beta-aminoisobuteric aciduria, an easily identified, genetically determined, biochemical abnormality of renal function that, as far as we can tell today, has absolutely no clinical consequences. In contrast, Line B depicts a genetic abnormality that causes inexorably progressive disease leading to the death of the patient. Examples of genetically determined diseases that follow the course shown by Line B and are usually lethal in adulthood are some of the lipidoses and hemoglobinopathies. Line C represents the course of a patient who has a genetic abnormality that, by itself, would be inconsequential and would probably never be detected unless external factors are introduced and make the deficiency evident. The classic example of this kind of abnormality is the person with glucose-6-phosphate dehydrogenase deficiency. Unless an afflicted person eats fava beans or is given various antimalarial drugs or other agents that induce a severe hemolytic reaction, he is completely asymptomatic and his genetic liability will probably remain undiscovered all his life.

Dr. Cohen has already indicated that the clinical course of the patient with genetically induced deficiency of A1T is unknown at present. Some investigators believe that patients with heterozygous deficiency follow Line A and that they are not predisposed to the development of obstructive lung disease.[38] Others believe that patients with homozygous deficiency follow Line B and hence are predisposed to the development of extensive destructive lung disease at an early age.[39] Another opinion, based primarily on the studies by Kueppers, Fallat, and Larson[26] and Lieberman and coworkers,[27] is that the pathway for *both* homozygotes and heterozygotes is that depicted by Line C. The genetic predisposition confers a vulnerability for the development of lung disease but external factors are presumably necessary to initiate the series of events that results in destruction of lung tissue. This is an important concept because, if subsequently proved, it underscores the importance of therapy directed at control of the external factors.

Of the conventional forms of treatment shown in Table 4, those that appear to be most valuable in the treatment of early (asymptomatic) chronic obstructive lung disease are directed toward the prevention of inflammation and the control of infection. Bronchodilators, expectorants, and the other remedies are *ex post facto,* since our

aim is to arrest the disease in its early stages before these remedies will be applicable. Prevention of inflammation and control of infection are applicable to both patients with A1T deficiency and patients with early emphysema or chronic bronchitis without a detectable biochemical abnormality because there is reason to believe that infection and inflammation of the airways and lung parenchyma are critically related to the progressive loss of pulmonary function.

It is mandatory that patients avoid all forms of tobacco. Smoking seems to be clearly the most important cause of widespread pulmonary inflammation, and cessation is probably the single most important preventive maneuver one can offer. The role of pollution from environmental sources has been difficult to characterize owing to its numerous complexities, but available evidence indicates that it does aggravate pulmonary function disturbances in patients who have underlying lung disease and that it can cause pulmonary inflammatory reactions. Therefore, air pollution could either initiate or compound a series of events that would culminate in more advanced lung disease.

Intercurrent lower respiratory tract infections are a frequent and troublesome problem in patients with asthma, chronic bronchitis, and emphysema. Respiratory infections are more prominent in these patients in the late stages of their illness, but careful questioning often reveals that unusually frequent and troublesome (compared with normal persons) "colds" or episodes of "bronchitis" have been present for many years or even decades. Whether or not patients with A1T deficiency are prone to frequent development of pulmonary infections has not been definitely established. However, all patients with documented early obstructive lung disease and those persons with biochemical abnormalities that may predispose to lung disease should be cautioned about the need for prompt and vigorous treatment of all infections of the lower respiratory tract. The earliest symptoms and signs of these infections are cough and the production of purulent sputum. Fever, leukocytosis, and changes detectable on chest roentgenograms are nearly always absent for the first several days and often are absent for the duration of the illness. Even though it is usually difficult to isolate a "pathogen" on sputum culture, cough and sputum production in these patients usually respond promptly to the administration of either tetracycline or ampicillin, especially if it is given early. It is possible that in the next few years additional antiviral agents, such as amantadine, will be available for the treatment of antecedent viral respiratory infections that seem to predispose to subsequent bacterial superinfection.

I should emphasize that these recommendations are based on unproved assumptions and that they are made from an optimistic viewpoint. We now have available diagnostic techniques that permit us to identify those patients with A1T deficiency that is associated with a high incidence of pulmonary emphysema and to detect by means of easily performed pulmonary function studies evidence of either breakdown of lung tissue or disease of small airways in asymptomatic patients. A preventive regimen comparable to that just outlined offers the best hope of inhibiting or arresting the disease process. We may hope that as additional patients with early disease or predisposing abnormalities are discovered and followed over the next several years, additional information will be discovered that can be used to control the epidemic of advanced and poorly treatable chronic obstructive lung diseases.

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CONCEALED POSTPARTUM HEMORRHAGE

A very serious postpartum hemorrhage that one may have to deal with and *can* deal with very effectively is the concealed hemorrhage, usually high in the vagina above the site of episiotomy. Typically one has delivered the baby, has perhaps repaired an extended episiotomy, gone home, and an hour later the patient (without any external bleeding) is in shock. The physician goes back to find a concealed hemorrhage high in the vagina. He can actually feel this rectally and vaginally. . . .

We have a method of treating this that I very much recommend. That is to open the episiotomy wide and attempt to evacuate. This is where suction would be helpful. Evacuate as much of this clot as you can. If you do not it will dissect all the way up retroperitoneally. Almost universally you will not find bleeding areas. At this point take a gall bladder drainage tube, one cut off so that it's just at the base of the cavity where you evacuate the hemorrhage; and bring it out of the buttocks and through the ischiorectal fat. Tie it with a suture to the skin and close that episiotomy tightly. They heal by primary intention. One actually has drainage through this. It may stay in about ten days. One actually can get out of what could be a very serious complication with a very nice result.

Needless to say the vagina is then packed tightly with as much gauze as you can use, and of course an indwelling catheter would be necessary. That pack is left in for 24 hours and blood is replaced.

—Isadore Dyer, M.D., New Orleans
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